REMARKS

Claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, and 42-44 were pending in the application, with claims 42 and 43 withdrawn from present consideration. Claims 1, 32, and 33 are amended. Claims 42 and 43, though presently withdrawn, show the same amendments for the Examiner's convenience in the event that the withdrawn claims are examined following allowance of the pending claims. Upon entry of these amendments, Claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, and 42-44 will be pending and under active consideration. Claims 1, 32, 33, 42, and 43 are independent.

Applicants submit respectfully that the amendments presented herein are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter. In particular, the expression "on both a base pair level and a repeat motif level" entered into claims 1, 32, 33, 42, and 43 is found at page 24, lines 20-21, of the specification as filed.

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action are respectfully requested.

I. The Examiner Interview

Applicants thank the Examiner, and the Examiner's supervisor, for the helpful interview conducted with Applicants' attorney on December 1, 2004. As noted in the Interview Summary, mailed December 3, 2004, the interview was attended by Robert Seabold, representing the Applicants, Cheyne Ly, the Examiner, and Ardin Marschel, the Examiner's supervisor. The focus of the interview was directed to the 35 U.S.C. § 103(a) rejection over U.S. Patent No. 5,619,991 to Sloane (hereinafter, "Sloane") in view of Hoe *et al.*, "Rapid Molecular Genetic

Subtyping of Serotype M1 Group A *Streptococcus* Strains" *Emerging Infectious Diseases*, 5:254-263 (1999) (hereinafter, "Hoe"), in further view of van Belkum *et al.*, "Variable Number of Tandem Repeats in Clinical Strains of *Haemophilus influenzae*" *Infection and Immunity*, 65:5017-5027 (1997) (hereinafter, "van Belkum '97"). The propriety of the combination of the references and the content of the Hoe and van Belkum '97 references were discussed at length. The Examiner's positions in regard to these issues are set forth below, followed by Applicants' responses in detail.

With regard to the propriety of the combination of Sloane, Hoe, and Van Belkum, the Examiner's position seemed to be that the primary reference, Sloane, teaches a networked system that employs epidemiological data to track infections and provide warnings based on analysis of that data, as allegedly taught in Sloane at column 2, lines 13-38. The Examiner suggested that the term "epidemiological data" should be construed broadly to encompass any type of disease/condition-related data, including sequence data taken from pathogenic bacteria. This broad construction of "epidemiological data" allegedly provides the motivation to combine Sloane with Hoe and van Belkum '97, which were suggested to teach sequencing methods for comparing strains of bacteria by analysis of VNTR sequences, thus allegedly reaching Applicants' claimed invention.

With regard to the content of the Hoe and van Belkum '97 references, the Examiner's position seemed to be that the combination of Hoe and van Belkum '97 teaches sequencing of bacterial DNA in VNTR regions and comparing the sequence data to discriminate between bacterial subtypes, thus reaching at least that portion of Applicants' invention. The Examiner pointed out that the claims as presented in Applicants' Amendment and Reply, filed October 14, 2004, allegedly are not limited to nucleotide sequence comparison rather than sequence length

comparison. The Examiner pointed to Table 2 in van Belkum '97 to show nucleotide sequence data and pointed to the Materials and Methods section of van Belkum '97, second paragraph, to show that sequencing was performed. In Hoe, the Examiner pointed to Figure 4 and passages in the text which allegedly show the use of sequencing of direct repeat regions as a means of comparing subtypes of bacteria. The Examiner also pointed out that the comparison of sequence data is allegedly old in the art.

II. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

A. The Propriety of Combining the References

Applicants maintain respectfully that the Office Action fails to describe sufficient motivation to combine the numerous references to reach Applicants' claimed invention. It is axiomatic in the patent law that motivation to combine references must be present within the references, themselves, and that without such motivation, the combination of references is improper. Applicants submit respectfully that the combination of three references, as presented in the rejection presented in paragraph 14 of the Office Action, much less five references as noted in the rejection presented in paragraph 37, requires that the Examiner bear a significant burden to show such motivation.

"It is impermissible to reconstruct the claimed invention from selected pieces of prior art absent some suggestion, teaching, or motivation in the prior art to do so." *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051-2, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988). Absent some teaching, suggestion, or motivation found within the references that the emulsions claimed by Applicants are desirable, it cannot be inferred that Applicants' invention would have been obvious to one of ordinary skill in the art. "It is insufficient to select from the prior art the

separate components of the inventor's combination, using the blueprint supplied by the inventor." *Interconnect Planning Corp. v. Feil,* 774 F.2d 1132, 1143, 227 USPQ2d 543, 551 (Fed. Cir. 1985).

Respectfully, Applicants maintain their position, evidenced in Applicants' previous submissions, that the Examiner has not carried the burden of showing motivation to combine the references cited against the present application's claims. In particular, Applicants submit respectfully that one skilled in the art at the time of the invention would not have deduced from Sloane that "epidemiological data," as discussed in Sloane (for example in the abstract and at column 2, lines 20-24) would include sequence data derived from infectious bacteria.

Further, one skilled in the art would not have been motivated to combine the methods of Hoe with the VNTR sequences of van Belkum '97. The methods of Hoe are directed to spacers between repeat regions, whereas the VNTR sequences of van Belkum '97 do not contain spacer regions. The absence of spacer regions in VNTR sequences is well known in the art, and may be deduced from van Belkum '97 by analysis of van Belkum '97 Table 2. As noted below, Table 2 discloses the existence of repeat units in VNTR regions, the length of each repeat unit, and the number of repeat units in a given VNTR. Also disclosed is the VNTR repeat location. Comparison of the position information with the repeat length an number reveals that the repeating units make up the entirety of the VNTR. For example, repeat code Hi 5-2 has 4 units of 5 bases each; thus, the VNTR should be 20 bases long if there are no spacers between the repeats. The repeat position is shown to between nucleotides 1368890-1368910, a length of 20 bases. Thus, Hoe cannot reasonably be combined with van Belkum '97.

B. The Rejection Over Sloane In View Of Hoe And van Belkum

1. Introductory Remarks

Claims 1, 3-5, 7, 12-14, 16, 17, 25-34, 36, and 44 stand rejected as allegedly being obvious over Sloane in view of Hoe and in further view of van Belkum '97" under 35 U.S.C. § 103(a). The Examiner alleges in sum that Sloane discloses an epidemiological database computer facility which collects and disburses medical, personal and epidemiological data. While the Examiner, in the Office Action mailed April 14, 2004, acknowledges that Sloane fails to teach the sequencing of VNTR regions and analyzing the obtained sequences for tracking the spread of infectious bacteria, the Examiner alleges that Hoe and van Belkum '97 cure these deficiencies. Allegedly, Hoe teaches methods of sequencing repeat regions, and van Belkum teaches analyzing VNTR regions to study bacterial pathogenesis, thus curing the deficiencies of Sloane Applicants continue to traverse, respectfully.

Applicants submit respectfully that the novel system and method for tracking and controlling infections of the present invention is neither taught nor suggested by Sloane, either alone or in combination with Hoe and van Belkum '97. In particular, there is neither teaching nor suggestion in these references of 1) an infection control system that may be used both to collect and analyze data and to provide warnings regarding epidemiological events or control the spread of disease, 2) a network that may be used to transmit disease and geographical data related to the pathogen (as opposed to data about the patient, as disclosed in Sloane), or 3) comparing the nucleotide sequence of repeats within VNTRs to compare and track pathogens. Thus, Applicants submit respectfully that, as neither Hoe nor van Belkum '97 cure the deficiencies of Sloane with respect to the rejected claims of the present invention, the combination of the cited references fails to meet the threshold required for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

2. The Sloane Reference

The Sloane reference discusses the use of computer networks in the transfer of *patient* information. The Office Action asserts that this patient information can be any information, including sequence data. However, the present inventive network as claimed transfers information about the disease pathogen isolates taken from patient or even an inanimate object or location, not information about the patient himself as described by Sloane. As indicated by Sloane at column 8, lines 2-17, "patient transaction records" are the source of data analyzed by the Sloane method. The presently-claimed invention relates to sequence information from *pathogens*, including those found on objects as well as on persons, and Sloane neither teaches nor suggests this.

Applicants submit respectfully that Sloane is directed to diagnosing and treating patients (see abstract, line 1), while the presently-claimed invention seeks to prevent and/or control the spread of disease-causing bacteria and prevent outbreaks related to that spread. Accordingly, the epidemiology that can be conducted with the Sloane system is of an entirely different sort than that of the present invention. As shown in Sloane at columns 2-4, the system of Sloane is directed to patient treatment as provided by an "e-doc." Column 2, lines 62-63, states that "Fig. 1 shows a number of entities involved in the delivery of health care." Column 3, lines 1-3, discusses "a physician 12 who delivers medical services for at least a segment of his/her patients using the principles of the present invention." Column 3, lines 10-14 describes a "medical database service 15 which is available to physicians and/or consumers to help diagnose and recommend treatment for diseases—particularly rare diseases with which the typical family practitioner may not be familiar."

By Sloane's method, as described at column 3, lines 48-50, a "patient 11 has a medical problem and wishes to consult with e-doc 12 to obtain advice and/or treatment." Columns 3-5 describe the collection of information from the patient: the e-doc collects patient "epidemiological data" including the patient's name, address, medical history billing and insurance information (see column 3, lines 54-60). Sloane's "epidemiological expert system" collects further information "which may be significant from an epidemiological standpoint," including "where he/she has eaten recently and what was eaten; whether he/she has traveled recently and, if so, to where and when; the name of a cruise ship ... the name of a professional meeting of conference that may have been attended" (column 4, lines 34-41). The type of data collected by Sloane's method is further described at column 6, line 60, to column 7, line 7, to include "a wide range of demographic data which may be of value to the CDC computer in terms of identifying epidemiological trends ... information about the person's residence ... whether or not the person uses a portable cellular phone, etc., any of which might have epidemiological ramifications."

Under some circumstances, the patient may be directed by the e-doc to visit a local lab which is "equipped to perform a wide range of conventional medical tests—blood, urine, sputum, etc.—as well as to provide inoculations" (column 5, lines 60-65). Results of such tests are attached to the patient's transaction record for use by the e-doc to diagnose the patient (see column 6, lines 5-15). Nowhere in the description does Sloane teach or suggest that pathogenic sequence data might be epidemiological data or that such data might even be collected. Applicants submit respectfully that, at the time of the invention, sequencing of pathogenic bacteria would not have been a "conventional medical test." Indeed, such sequencing is not a

conventional medical test today. It seems clear that the methods of Sloane are directed to patient/doctor interactions facilitated by the internet.

Furthermore, the Sloane system does not disclose providing warnings of potential disease outbreaks. As indicated by Sloane at column 8, lines 9-12, the Sloane system reports data to an outside organization (not part of the system) that may assist the external organization (*i.e.*, the CDC) to provide reports or treatment options to affected persons or groups. Thus, Applicants submit respectfully that Sloane does not teach or suggest a system that provides warnings regarding epidemiological events.

With regard to non-sequence data transmitted by the system of Sloane, the system is described as transmitting data that identifies people in a geographical area that have the same illness in order to find an outbreak (see column 2, lines 30-39). Sloane's database contains geographic information about the patient, but Sloane only recites that the database might contain patient information such as the patient's address for billing purposes (see paragraph bridging columns 6-7, for example)-- there is no suggestion that the Sloane database would track the current location of the patient or the current location of the pathogen. On the other hand, the presently-claimed invention determines an outbreak according to the location where a bacterial isolate is collected and using the genetic similarity of the pathogens as determined through sequence data comparison. Accordingly, Applicants submit respectfully that Sloane's disclosures are over-broad and do not suggest the same use of networking that the present invention uses.

3. The van Belkum '97 Reference

The Examiner, as noted above, acknowledges that Sloane fails to teach the use of the nucleotide sequence of VNTR sequences for tracking the spread of infectious bacteria.

However, the Examiner alleges that Hoe and van Belkum '97 cure these deficiencies. Applicants submit respectfully that neither Hoe nor van Belkum '97 teach or suggest the use of VNTR sequence data as disclosed and claimed by Applicants. As described at length in the present specification as filed, particularly at page 22, lines 20-21, page 24, lines 20-21, page 28, line 15, to page 30, line 4, the presently-claimed system uses a method of sequencing, and comparing the nucleotide sequence of, distinct "cassettes," or "repeat sequences," present in variable number and arrangement within VNTR regions of the pathogenic genome. The actual sequence of nucleotides within these cassettes is the basic element for the present-inventive comparison between bacterial isolates.

Van Belkum '97, contrary to the presently-claimed invention, ***does not*** use the sequence of the repeat cassettes to compare pathogens. Van Belkum '97 analyzes the ***length and/or number*** of repeat sequences in repeat regions and does not teach or suggest the analysis of the sequence within the repeat cassettes or a comparison of the type of cassette. For example, figures 1 and 2 of van Belkum '97 show the comparison of the total length of the repeat region for various isolates. Tables 3 and 4 show the number of repeats in various pathogen strains.

As noted above, the Examiner has pointed out that the Materials and Methods section of van Belkum '97, at page 5018, second full paragraph, allegedly discloses sequencing of a VNTR region. The Examiner further pointed to Table 2 in van Belkum '97 to show nucleotide sequence data from VNTRs. Applicants rebut these allegations as follows.

The cited passage from the Materials and Methods section of van Belkum '97 discloses that a "whole genome sequence as determined for *H. influenzae* (GenBank accession number L42023) was screened with a newly developed algorithm" (van Belkum '97, page 5018, lines 38-40). Applicants noted respectfully that the cited passage does not disclose that sequencing was

actually performed for the isolates analyzed in van Belkum '97. This position is supported by the fact that the Materials and Methods section does **not** recite materials and methods for conducting sequencing. Likewise, the entire text of van Belkum '97 fails to discuss nucleotide sequence data. However, the section does disclose materials and methods for conducting PCR analysis of the length of VNTR regions (page 5018, fourth full paragraph).

The reason for conducting the computer-aided VNTR searches, as noted in the Results section of van Belkum '97, was to substantiate the existence of VNTR regions in the subject bacteria and to design PCR primers for amplifying those regions to assess their length. Table 2, cited by the Examiner, shows "the result of the computer-aided searches" for VNTRs (page 5018, lines 4-5). Table 2 discloses the existence of various repeat units, each of which is identified by code (Hi 2-1 through Hi 6-3). "Primers for tracking repeat variability were designed for all of the potential VNTRs of *H. influenzae* (Table 2). The 20 nucleotide primers were selected on the basis of positional criteria only, their location being 5 nucleotides upstream and downstream of potential VNTRs" (page 5018, lines 30-35). PCR amplification of the VNTR regions is performed, and the "average lengths of the repeats and the observed variation in length are given in Table 3" (page 5018, lines 50-52).

Applicants submit respectfully that van Belkum '97 fails to disclose sequencing of isolates. The repeat unit sequences disclosed in Table 2 were derived from computer-aided analysis of a GenBank sequence, and primers were constructed according to the GenBank sequence as well. Accordingly, van Belkum '97 does not teach or even suggest sequencing the individual isolates. In fact, there is no way to know from the disclosures of van Belkum '97 that the DNA amplified by PCR even contains the unit sequences disclosed in Table 2, much less

whether there is any nucleotide variability within those unit sequences. van Belkum '97 merely analyzes the length of PCR products.

That van Belkum '97's methods are directed solely to VNTR region length is indicated repeatedly within the text, and each and every example of raw data (electrophoresis gel photographs) provides information solely with regard to the length of PCR products. For example, "Table 3 shows that changes in the size of a given repeat did not coincide with similar changes in other repeats" (page 5019, column 1, lines 4-6). "All other VNTR regions showed fragment length variability. Five of the VNTR analyses provided clear length polymorphisms" (page 5019, column 2, line 7, to page 5021, column 1, line 1). "An overview of repeat length polymorphisms for the tetranucleotide repeats is provided in Table 5" (page 5021, column 2, lines 38-39). It should be noted that the term "polymorphism," as used in van Belkum '97, relates solely to VNTR length polymorphism and not to nucleotide sequence polymorphism (no sequencing was performed).

Accordingly, Applicants submit respectfully that van Belkum '97 cannot be deemed to teach or suggest the analysis of repeat unit nucleotide sequence to differentiate amongst individual bacterial isolates. van Belkum '97 teaches that VNTR length polymorphism is significant: "changing the repeat length has documented effects on virulence" (page 5024, column 1, lines 8-9). However, van Belkum '97 does not teach or even suggest that the sequence within the repeat units is significant. van Belkum '97 teaches that PCR (rather than sequence) analysis is important. In fact, van Belkum '97 teaches that the sequence of adjacent DNA (and not VNTR sequence) is the only important sequence. "Once the DNA sequences of the VNTR-bordering PCR primers have been determined and found to be species-specific, both diagnostic

information and data on the evolutionary status of the strains involved can be obtained by performing a single PCR test." (van Belkum '97, page 5025, column 2, lines 14-18).

Even further, van Belkum '97 teaches that nucleotide sequence changes within repeat units are insignificant. "[I]t is important to realize that VNTRs greatly differing in length can still give rise to the same phenotype. When a gene contains a tetranucleotide VNTR and is switched on when seven copies of the repeat unit are present, the gene will be expressed in a comparable fashion when $7 \pm 3n$ copies of the element are present." (van Belkum '97, page 5025, column 1, lines 20-27). Clearly, van Belkum '97 does not account for phenotypic differences that may be due to nucleotide changes within repeat units. Such changes *are* accounted for and analyzed in the presently-claimed invention.

4. The Hoe Reference

The Hoe reference is cited by the Examiner to teach sequencing of repeat units in the analysis of bacterial subtypes. However, Hoe analyzes the sequences between direct repeat units rather than the repeat units themselves. Figure 4 of Hoe, for example, shows the various differences in the spacer regions between DR (direct repeat) elements without analysis of the DR sequences, themselves. While the figure shows the sequence for the DR element (Figure 4, part A), the figure indicates that the sequence of the DR elements is identical in all cases. Therefore, Hoe teaches away from the analysis of the nucleotide sequence of the repeats, themselves. Again, the method of the present invention, which compares the sequence within repeat cassettes, is neither taught nor suggested by Hoe.

It should be noted that Hoe discloses sequence analysis of the *emm* and *sic* genes in Group A *Streptococcus*, but these genes do not contain repeat sequences of any kind.

Accordingly, the inference that Hoe teaches away from analyzing the sequence within repeats is strengthened; Hoe fails to perform the same sequence analysis of the DR elements accorded to the *emm* and *sic* genes. Hoe only analyzes sequence *between* repeats.

Furthermore, it should be noted that direct repeat (DR) sequences ***are not*** VNTRs. DR sequences are well known in the art as having *identical* sequence in each of the repeated subunit cassette elements. Furthermore, as noted above, VNTRs do not include spacer regions as do the DR sequences of Hoe. Hoe showed that the spacer region between the elements may vary, but Hoe fails to disclose that the sequence of the cassette elements, themselves, might vary or be useful in an analysis for determining bacterial subtypes.

Accordingly, Applicants submit respectfully that neither Hoe nor van Belkum '97, alone or in combination, teach or suggest Applicants' methods of tracking infection by comparing the sequences of VNTR repeats. As the Examiner admits that Sloane, alone, does not teach the Applicants' methods, Applicants submit respectfully that the combination of Sloane with Hoe and van Belkum '97 cannot be deemed to disclose Applicants' claimed methods. Furthermore, Applicants submit respectfully that the combination of these references is improper an any case. Accordingly, Applicants submit respectfully that the combination of Sloane with Hoe and van Belkum '97 fails to meet the threshold required for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

In view of the above, Applicants submit respectfully that the rejection of claims 1, 3-5, 7, 12-14, 16, 17, 25-34, 36, and 44 under 35 U.S.C. § 103(a) have been overcome, and Applicants request respectfully that the rejection of claims 1, 3-5, 7, 12-14, 16, 17, 25-34, 36, and 44 under 35 U.S.C. § 103(a) be withdrawn.

B. The Rejection Over Sloane In View Of Hoe, van Belkum, O'Brien, And Paradiso

The Examiner has maintained the, rejection of claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, and 44 as allegedly being obvious over Sloane in view of Hoe and van Belkum '97 and further in view of O'Brien *et al.*, *Chest*, 112: 387-392 (hereinafter, "O'Brien") and U.S. Patent No. 6,404,340 to Paradiso *et al.* (hereinafter, "Paradiso")(in sum, the "Cited References"), under 35 U.S.C. § 103(a) for the reasons of record as noted in the Office Action. In sum, the Office Action alleges that the combination of Sloane in view of Hoe and van Belkum '97 teaches all the limitations of the claims rejected above, but fails to teach the additional limitations of claims 8, 10, 11, 22-24, 35, and 38. The Office Action alleges that O'Brien and Paradiso cure these deficiencies. Applicants traverse respectfully.

Without acquiescing in the propriety of the allegations based upon the disclosures of O'Brien and Paradiso, Applicants submit respectfully that the novel systems and methods for tracking and controlling infections of the present invention are neither taught nor suggested by any of the Cited References, either alone or in any combination. As noted above, Sloane neither teaches nor suggests that 1) an infection control system that may be used both to collect and analyze data and to provide warnings regarding epidemiological events or control the spread of disease, 2) a network that may be used to transmit disease and geographical data related to the pathogen (as opposed to data about the patient, as disclosed in Sloane), or 3) comparing the nucleotide sequence of repeats within VNTRs to compare and track pathogens. As presented above, neither Hoe nor van Belkum '97 cure these deficiencies, and the Examiner does not allege that O'Brien and/or Paradiso cure these deficiencies. Thus, Applicants submit respectfully that

combination of the Cited References fails to meet the threshold required for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

With particular regard to claim 16, Applicants submit respectfully that, in addition to all of the reasons noted above, claim 16 is patentable over the cited references because none of the cited references discloses "treating the insertion or deletion of a repeat sequence as a single genetic event" as recited in claim 16.

Accordingly, Applicants submit respectfully that the rejection of Claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, and 44 under 35 U.S.C. § 103(a) have been traversed, and Applicants request respectfully that the rejection of Claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, and 44 under 35 U.S.C. § 103(a) be withdrawn.

AUTHORIZATION

Applicants believe there is no fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 19-5127 (Order No. 19124.0002) or credit any overpayment to same.

CONCLUSION

Applicants submit respectfully that the present application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

If the Examiner feels that an interview would facilitate the prosecution of this application, Applicants respectfully urge the Examiner to contact the undersigned directly at 202-295-8466.

In general, Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 424-7500. All correspondence should be directed to our address given below.

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